

MINI REVIEW

Drug development and open access: approaches and perspectives

Dmitri V. Debabov¹, Maria D. Debabova²

¹ NovaBay Pharmaceuticals, Inc., Emeryville, CA, USA

² Scientific electronic library eLIBRARY, Moscow, Russian Federation

Corresponding author: Maria Debabova, e-mail: rationiac@gmail.com

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ABSTRACT

The development of a new medicine is a process that requires enormous time and tremendous financing. It takes 10-15 years from the discovery of an active compound to the launch of its production and the start of drug marketing with the total costs of the project reaching 1.8 billion US dollars. These large time and financial costs stem from repeated testing and elimination of a large percentage of compounds over the course of screening at each stage of preclinical and clinical trials. Many investors have lost interest in financing new drug discovery projects (or pharmaceutical start-up companies) due to the high risk and extensive time required to produce a return on investments. Since all the research data are considered confidential by pharmaceutical companies and thus never shared with scientific community, different scientific groups waste significant resources repeating the same costly experiments in drug discovery. In this article, we discuss new approaches to drug discovery involving open access to the research data and alternative financing that could significantly streamline the search for new cures for human diseases.

Proposals for open access to scientific data in drug development

The data collected in the course of drug development projects in pharmaceutical companies are confidential and are not shared within scientific community. That often leads to repetition of the efforts of various research groups in different companies. Open access publication of these data would save the costs of the synthesis and testing of compounds that have already been tested by other scientists. The prospect of significant resource savings exists – it is the development of new drugs in an open access format [1].

Large pharmaceutical corporations often collaborate with small innovative firms or academic groups and acquire rights to new substances or technologies. This approach is called open innovation. It is certainly a step forward compared to the development of a drug within a single firm, but the number of researchers with access to information remains limited.

Recently, there are more attempts to open the access to research data in drug development to scientific community. This approach is especially effective at the early stages of drug discovery, when scientists are searching for and validating new targets [2].

A striking example is the Structural Genomics Consortium (SGC) that was founded in 2003. According to the SGC rules, the general public has free access to all the results including the DNA sequences and the structures

of the chemical compounds obtained by scientists participating in the project. SGC has received the support of hundreds of companies and academic groups. Thanks to this project, the scientific community today has the opportunity to work with thousands of interesting substances and samples. Hundreds of articles have been published, that, for example, led to discovery of selective inhibitors for G9a-like protein (GLP) lysine methyltransferase [3]. One of the successful examples of collaboration between SGC and GlaxoSmithKline is development of the free web-based interactive tools *WONKA* and *OOMPPAA* that help to analyze the protein-ligand interactions using computation chemistry approach [4]. Another example of successful collaboration between GlaxoSmithKline and SGC is the study of JQ1 – an inhibitor of Bromodomain and Extra-Terminal motif (BET) family of bromodomain proteins – in cell and animal models. Results of this project were shared with scientific community and the inhibitor became available to other research groups. That facilitated the launch of several research programs in biopharmaceutical companies. These programs were focused on search for the new BET inhibitors with anti-cancer, immunosuppressive and other medicinal effects. Some of these programs resulted in discovery of new structurally related potent BET inhibitors and led to a number of ongoing clinical trials [5].

It is particularly interesting that open research projects, especially those that focus on searching for a therapy for rare diseases, are often financed by groups of patients and

their relatives. One of the examples of the rare diseases is progressive ossifying fibrodysplasia (fibrodysplasia ossificans progressiva, FOP), also known as second skeleton disease, or one of the forms of glycogenase type IV (adult polyglucosan body disease, APBD), which are often fatal or lead to the disability of the patient. However, the number of people suffering from these diseases is small (hundreds or thousands in the world), which makes these areas of drug development unprofitable for pharmaceutical companies. The collaboration between the patients' groups and scientists could lead to significant acceleration of drug discovery and development process for this class of drugs.

There are a number of successful examples of collaborations between the patients' advocacy groups such as the Michael J. Fox Foundation for Parkinson's Disease Research and the Cystic Fibrosis Foundation and biopharmaceutical companies. These public organizations finance the initial research programs in biopharmaceutical companies, provide access to the corresponding disease experts and help with clinical trials recruitment. Financing of the first stage of drug discovery process and supporting the data sharing throughout the whole process both significantly help to accelerate the development of new drugs for rare diseases [6].

Open platforms for the discovery of therapeutic targets

Several scientific organizations and pharmaceutical companies including Biogen, The European Molecular Biology Laboratory – European Bioinformatics Institute (EMBL-EBI), GlaxoSmithKline, and Wellcome Trust Sanger Institute have recently created an open platform Open Targets for the discovery and validation of new therapeutic targets [7].

This platform enables open access to genomics, proteomics, the results of traditional biochemical experiments, animal models for corresponding diseases, clinical data, *etc.* in order to find and validate certain targets (genes or proteins) as the first step in the course of the drug discovery process for the corresponding disease.

Antibiotics and open access

Antibiotic resistance in the past few decades has produced a real health crisis. Uncontrolled use of these drugs in medicine and agriculture has led to a selection of resistant microorganisms. At the same time, the rate of discovery of new antibiotics slowed down significantly.

There are some economic reasons for that: the expenditure of time and money for the discovery and development of new drugs is very high while the potential profits from antibiotics are low compared with so-called blockbuster drugs, *e.g.* Viagra®. On the other hand, "all the low-hanging fruit has already been ripped off" [8]. Most known classes of antibiotics were discovered in the 1950–1970s as a result of screening of natural products. Today, in order to find new active compounds, scientists have to work with microorganisms that were previously uncultivated. In addition, the general drawback of all "natural" antibiotics is that they are likely to have mechanisms of resistance already.

However, millions of compounds that are not found in nature and have never been tested for antimicrobial activity have already been synthesized in chemical labs around the world. The Chemical Abstract Service (CAS) has around 100 million organic compounds registered [9]. Chemists in universities and industrial scientific laboratories synthesize thousands of new compounds every year. For the most part, these products are not designed as drug candidates, but are rather synthesized for other purposes, *e.g.* to develop new methods of organic synthesis. Therefore, unlike the libraries of substances created by pharmaceutical companies specifically to search for certain types of medicines, their diversity is practically unlimited. For example, if you apply to the collection of all the CAS registered organic compounds the general set of physicochemical restrictions for antimicrobials ($MW < 1200$ Da and $\log P$ between -10 and 2) [10] about one third of all the compounds will be selected for the further screening. Are there any promising new antibiotics among all this diversity?

In order to answer this question, the community for the antimicrobial drug discovery that is based on the principles of free access to research data was established, Community for Open Antimicrobial Drug Discovery (CO-ADD). This organization is funded by the Wellcome Trust and the University of Queensland (Brisbane, Australia) [9].

Any chemist in the world can send samples that will be tested free of charge for activity against several key microbial pathogens, cytotoxicity and protein binding. In addition, some other properties of these compounds, which are important for their antimicrobial activity, will be studied. All the expenses for weighing, packaging, and shipment of the samples are covered by CO-ADD. If a prospective antimicrobial compound is found, its further optimization requires funding through various grants.

All the compounds included in this program are tested by the same standard methods, which is important for comparing the results. Moreover, negative results are considered to be as important as the positive ones. As the data accumulates, the value of this program will only increase as it becomes possible to establish new correlations between the structure of various compounds and their properties such as antimicrobial activity, ability to penetrate into microbial cells, and cytotoxicity.

In order to attract to the project as many scientists as possible, CO-ADD uses advertising and search engine optimization (Google AdWords), social networks as well as campaigns in the media [11].

One of the successful examples of CO-ADD cooperation with Russian research organizations is its collaboration with the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences (ZIOC RAS). Scientists from this institute agreed to provide the CO-ADD with 150,000 substances selected using nuclear magnetic resonance for screening. Of these, 35,520 substances have already been shipped for testing and several "hits" – substances with interesting antimicrobial activity and selectivity – have been discovered. That marks the starting point for the further optimization of the molecular structure of the drug candidate.

Open access drug development and intellectual property

Intellectual property is an important source of income for universities and pharmaceutical companies. At present, almost every university has a patent office, which is extremely reluctant to share research results. Usually this requires the negotiation of contracts, which can take several months.

CO-ADD offers a reasonable compromise between the protection of intellectual property and open access to scientific data. After testing, the researchers have one and a half years to file a patent for their compound (if necessary, this term can be extended by mutual agreement). After that, the scientists are required to provide a publication for an open access database.

CONCLUSIONS

Restrictions in the free distribution of information in drug development, including the patent system can slow down drug discovery efforts. At the same time, it is imperative to expedite the search for new antibiotics and cures for various lethal diseases. For example, there are well-known legal proceedings related to the patenting of human DNA sections, particularly genes responsible for the oncological diseases [12]. The time and resources spent by universities, pharmaceutical companies, and scientists for legal cases in patent courts, which are caused by the existing system of research data confidentiality, probably could be used much more effectively.

REFERENCES

1. Arshad Z, Smith J, Roberts M, Lee WH, Davies B, Bure K, et al. Open Access Could Transform Drug Discovery: A Case Study of JQ1. *Expert Opin Drug Discov.* 2016; 11(3), 321-32. doi: 10.1517/17460441.2016.1144587.
2. Lee WH. Open access target validation is a more efficient way to accelerate drug discovery. *PLoS Biol.* 2015; 13(6), e1002164. doi: 10.1371/journal.pbio.1002164.
3. Xiong Y, Li F, Babault N, Dong A, Zeng H, Wu H, et al. Discovery of Potent and Selective Inhibitors for G9a-Like Protein (GLP) Lysine Methyltransferase. *J Med Chem.* 2017; 60(5), 1876-91. doi: 10.1021/acs.jmedchem.6b01645.
4. Deane CM, Wall ID, Green DV, Marsden BD, Bradley AR. WONKA and OMMPPAA: analysis of protein-ligand interaction data to direct structure-based drug design. *Acta Crystallogr D Struct Biol.* 2017; 73(3), 279-85. doi: 10.1107/S2059798316009529.
5. *Drug Discovery in Cancer Epigenetics (Translational Epigenetics Series)*. 1st ed. G. Egger, P. Arimondo (eds.). Elsevier, 2016. doi: 10.1016/C2014-0-02189-2.
6. Litterman NK, Rhee M, Swinney DC, and Ekins S. Collaboration for rare disease drug discovery research [version 1; referees: 2 approved]. *F1000Research.* 2014; 3, 261. doi: 10.12688/f1000research.5564.1
7. Koscielny G, An P, Carvalho-Silva D, Cham JA, Fumis L, Gasparyan R, et al. Open Targets: a platform for therapeutic target identification and validation. *Nucleic Acids Res.* 2017; 45(D1), D985-D994. doi: 10.1093/nar/gkw1055.
8. Cooper MA. A community-based approach to new antibiotic discovery. *Nat Rev Drug Discov.* 2015; 14(9), 587-8. doi: 10.1038/nrd4706.
9. Hansford KA, Blaskovich MA, Cooper MA. Chemical philanthropy: a path forward for antibiotic discovery? *Future Med Chem.* 2016; 8(9), 925-9. doi: 10.4155/fmc-2016-0029.
10. O'Shea R, Moser HE. Physicochemical properties of antibacterial compounds: implications for drug discovery. *J Med Chem.* 2008; 51(10), 2871-8. doi: 10.1021/jm700967e.
11. Desselle MR, Neale R, Hansford KA, Zuegg J, Elliott AG, Cooper MA, et al. Institutional profile: Community for Open Antimicrobial Drug Discovery – crowdsourcing new antibiotics and antifungals. *Future Sci OA.* 2017; 3(2), FSO171. doi: 10.4155/foa-2016-0093.
12. US Supreme Court says human DNA cannot be patented. Available: https://www.bbc.com/russian/science/2013/06/130613_us_supreme_court_genes

The open access approach to research data in drug discovery and development projects has significant economic prospects. Most importantly, it enables small institutions and firms, start-up companies, researchers, non-profit organizations, and other interested parties around the world to take part in the scientific process that is focused on an extremely important goal – supporting the life and health of all humans.

CONFLICT OF INTEREST

The authors do not pursue any commercial or financial interests.

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